REMARKS

Claim Status

Claims 21, 24, 26, 30 and 36-42 are pending in this application. Claims 30 and 40-42 are objected to as being dependent on a rejected base claim, but are indicated to be allowable if rewritten in independent form. Claim 40 is amended herein to independent form. New claims 43-49 are introduced herein. Support for new claims 43-49 is provided by the specification at, e.g., paragraphs [0078], [0079], [0489], and by the claims as filed. No new matter is added by way of the claim amendments or new claims. Entry of the claim amendments and new claims, and reconsideration in view of the following remarks are respectfully requested. Claims 21, 24, 26, 30 and 36-49 are now pending and under examination.

Claim Objections

Claims 30 and 40-42 are objected to as being dependent on a rejected base claim. Applicants thank the Examiner for the indication that claims 30 and 40-42 are allowable if rewritten in independent form, including all the limitations of any intervening claims.

Claim 40 is rewritten herein in independent form, including all the limitations of claim 21 from which it depended. Accordingly, claim 40 as amended is allowable. New claims 43-49 are added herein that properly depend from claim 40. The Applicants respectfully submit that claims 41-49 are also allowable, as they depend from and further limit an allowable claim.

Rejections under 35 U.S.C. § 103

Claims 21, 24, 26 and 36-39 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Chamberlain et al. (US 2005/0234083) in view of Klaviniskis et al. (US 2003/0147923) and Ryan (US 4,171,353) for reasons of record. Applicants traverse the rejections for reasons of record, as well as at least the following reasons.

The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 82 USPQ2d 1385, 1396 (2007) re-emphasized the requirement that the *Graham* factors be evaluated in determining

whether the claimed invention is obvious. As the Office is, of course, aware, the *Graham* factors require determination of 1) the scope and content of the prior art, 2) the level of skill of the ordinary practitioner of the art, and 3) the nature of the differences between the prior art and the claimed invention. It must then be evaluated, as a matter of law, whether these differences would or would not have been obvious to the skilled artisan, taking account of any objective evidence of nonobviousness.

The scope and content of the cited art have been addressed at length, and this discussion will not be reiterated in detail here. Briefly, Chamberlain et al. are said to disclose benzimidazoles useful for the treatment of hyperproliferative diseases (Abstract), including breast and colon cancer. Chamberlain et al. are further said to disclose that their compounds can be employed alone or in combination with other therapeutic agents, such as other chemotherapeutic, hormonal, or antibody agents (paragraph [0414]), and may be prepared as oil-in-water emulsions (paragraph [0394]). The Examiner has acknowledged that Chamberlain et al. fail to specifically disclose use in combination with an antigen (see Office Action at page 5). Ryan is cited for the proposition that oil-in-water emulsion type adjuvants are known to enhance immune responses in animals and are capable of providing a slow release of the antigen (col. 1, lines 26-39).

Klaviniskis et al. are said to disclose a composition containing spores of *Bacillus subtilis* in an amount effective to stimulate immune responsiveness in a subject, wherein the spores may have an adjuvant effect, and may be used as an adjuvant in vaccine compositions which optionally contain an antigen (Abstract). Klaviniskis et al. is further said to disclose that, because the spores stimulate cell-mediated immune responses, administration of the spores with cancer vaccine components can be used to treat cancers, including colon and breast cancers (paragraph [0083]).

The instant Office Action again fails to identify the identity and skill level of the 'person having ordinary skill in the art' (i.e., "the PHOSITA"). As the outstanding rejections are for obviousness, Applicants respectfully submit that determination of the PHOSITA is essential to correctly ascertaining the obviousness or nonobviousness of the claimed invention over the cited art. As previously discussed in an interview conducted on August 26, 2008 between Examiner Chong

and the Applicant's representative, Michael G. Smith, the Applicant's representative suggested the PHOSITA might be a medical practitioner, i.e., a physician treating a patient, but no definitive agreement was reached with respect to this issue. Applicants again request that the Examiner clearly identify the level of a skill of the ordinary practitioner of the art so that the record can be made complete for appeal.

The Office has improperly disregarded express claim limitations

At the outset, it is necessary to properly construe the claims in order to compare the invention as claimed with the cited art. The Examiner has again refused to afford patentable weight to the term "vaccine" in the claim preamble, on the grounds that this is merely a recitation of purpose or intended use. In maintaining this position, the Examiner has also improperly disregarded express claim limitations in claims 21 and 26 regarding the "amount effective to enhance the immune response in a subject to the antigen" (claim 21) and "wherein the immune response is the cellular production of one or more cytokines" (claim 26), on the basis that these limitations are somehow *inherent* in the composition itself. The Applicants respectfully disagree.

The Examiner has failed to read the claim preamble in the context of the entire claim. "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999). MPEP 2111.01. "During prosecution, statements in the preamble reciting the purpose or intended use of the claimed invention must be evaluated to determine whether the recited purpose or intended use results in a structural difference (or, in the case of process claims, manipulative difference) between the claimed invention and the prior art. If so, the recitation serves to limit the claim." See, e.g., *In re Otto*, 312 F.2d 937, 938, 136 USPQ 458, 459 (CCPA 1963); MPEP § 2111.02(II).

As disclosed in the specification at, e.g., paragraph [0490], the invention is directed to administering immunogenic compositions, wherein the vaccine is administered in an amount effective to stimulate an immune response. As explained in the specification at, e.g., paragraph

[0133], such enhanced immune-response eliciting compositions generally comprise an antigen and an adjuvant, e.g., for use in a vaccine composition. The effective amount depends, *inter alia*, on the amount and identity of the adjuvant administered and the immune response to be enhanced (e.g., a cell mediated response, such as cytokine production), and can be readily determined by those of ordinary skill in the art. See specification at, e.g., paragraph [0490]. Thus, the fact that the claimed compositions are vaccine compositions is necessary to give meaning to the express limitations in the body of claims 21 and 26, which have been improperly disregarded by the Examiner.

Moreover, the fact that the claimed compositions are vaccine compositions limits the structure of the claimed compositions to those wherein the adjuvant is present in an amount effective to enhance the immune response. Accordingly, the recitation in the claim preamble should be afforded patentable weight in assessing the differences between the cited documents and the claimed invention as a whole.

Regardless of the patentable weight afforded to the term "vaccine" in the claim preamble, the Examiner has improperly ignored the functional limitation in claim 21 (and the claims which depend thereon) requiring that the adjuvant be present in "an amount effective to enhance the immune response in a subject to the antigen," as well as the limitation in claim 26 requiring that "the immune response is the cellular production of one or more cytokines." These limitations clearly distinguish the claimed invention from the cited art, and the Examiner has pointed to nothing in the art that teaches or otherwise suggests these features of the instant invention.

The Examiner asserts that these claim limitations recite inherent properties, and are not entitled to patentable weight, because "[p]roducts of identical chemical composition can not have mutual exclusive properties. Any properties exhibited by or benefits from are not given any patentable weight over the prior art provided the composition is inherent. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the disclosed properties are necessarily present." *In re Spada, 911* F.2d 705, 709, 15 USPQ 1655,1658 (Fed. Cir. 1990) (emphasis added). See MPEP 2112.01.

As previously noted by the Applicants and as acknowledged by the Examiner, the prior art does not teach compositions identical to claimed vaccine compositions, which include both a benzazole adjuvant in an amount effective to enhance an immune response and an antigen. The Examiner is correct that something old does not become patentable upon discovery of a new property. However, this is irrelevant to the facts of the present case. The claimed vaccine compositions were not known in the prior art, and the properties of unknown compositions (inherent or otherwise) cannot be considered to have been present in the prior art. "Obviousness cannot be predicated on what is not known at the time an invention is made, even if the inherency of a certain feature is later established." *In re Rijckaert*, 9 F.2d 1531, 28 USPQ2d 1955 (Fed. Cir. 1993); MPEP 2141.02(V). Clearly, the "inherent" properties of *hypothetical* compositions cannot properly be relied upon to establish obviousness.

It is well-settled law that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy,* 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). MPEP §2112(IV). "Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

In the instant case, the Office has failed to meet its burden of proof in establishing a basis in fact or technical reasoning that would lead one of skill in the art to conclude that the properties of the claimed vaccine compositions, and in particular the limitation that the adjuvant is present in an amount effective to enhance an immune response to the antigen, would necessarily be present in the Examiner's proposed combination of an oil-in-water emulsion of a compound of Chamberlain et al. and an antigen, as in Klaviniskis et al.

There is no motivation to combine the cited art in the manner claimed

The Examiner asserts that a person of ordinary skill would have been motivated to combine the antigens of Klaviniskis et al. with an oil-in-water emulsion composition of

Chamberlain et al. because: "(1) Chamberlain and Klaviniskis et al. are analogous art since both disclose a method of treating colon and breast cancers; (2) Chamberlain et al. teaches that other therapeutic agents may be employed in anticancer therapy; (3) Klaviniskis et al. disclose a composition comprising spores, which contain adjuvants that have an immunomodulatory effect and stimulates immune responsiveness; and (4) Chamberlain et al. discloses oil-in-water emulsion, which are well-known immunological adjuvants that provide slow release of the antigen." (Office Action at page 6.) The Applicants respectfully disagree.

Regardless of Ryan's disclosure that oil-in-water emulsion adjuvants are known (col. 1, lines 26-39), the Office has provided no explanation why one of ordinary skill in the art would conclude, *a priori*, that the particular, oil-in-water emulsions disclosed by Chamberlain et al. would be useful as oil-in-water emulsion adjuvants. Nor has the Examiner provided any basis to support the conclusion that one of skill in the art would consider all oil-in-water emulsions to be useful as oil-in-water emulsion adjuvants. In the absence of such a conclusion, the cited references provide no motivation that would lead one of skill in the art to include these compounds in combination with an antigen in an amount effective to enhance an immune response to the antigen. Moreover, in view of the disclosure of Klaviniskis et al. regarding the problems associated with other adjuvants (see, e.g., paragraphs [0007]-[0011] and [0014]), the Examiner has pointed to nothing that would lead one of skill in the art to reasonably conclude that the *B. subtilis* spores in Klaviniskis et al. could be replaced by another adjuvant while retaining the disclosed activity.

As the MPEP makes clear, "[t]he key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 82 USPQ2d 1385, 1396 (2007) noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit." MPEP § 2142. As noted in the memorandum from the Deputy Commissioner, issued immediately in response to the *KSR* decision, in formulating a rejection for obviousness based on a combination of elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed.

For the sake of argument, even if one assumes that the cited art could be considered to suggest that it would be desirable to administer to a subject both a compound of Chamberlain et al. having an anti-cancer effect and an antigen or vaccine composition, according to Klaviniskis et al., a major difference between the teachings of the cited documents and the invention as claimed requires that the small molecule compound and the antigen be formulated as a vaccine composition, i.e., mixed together, wherein the small molecule compound functions as an adjuvant and is present in an amount effective to enhance the immune response to the antigen. These claim limitations, which are not suggested by the cited art, clearly distinguish the claimed invention as a whole from the cited art, and have been improperly disregarded by the Examiner.

In the present case, no real reason has been provided why one of skill in the art would physically combine the compounds of Chamberlain et al. with the antigens of Klaviniskis et al., and no advantage of mixing them together has been identified. The Examiner relies on a statement by Chamberlain et al. that the compounds can be used 'in combination with' other active agents (exemplified by chemotherapeutic agents, hormones or antibody agents), and cites *In re Kerkhoven*. The cited portion of Chamberlain does not disclose or suggest that the other agent should be mixed with Chamberlain's compound, nor does it say the other active agent could be an antigen or vaccine. No rationale has been provided to explain why this general statement would lead one of ordinary skill to combine Chamberlain's compounds into a single composition with Klaviniskis' antigens. The justification for physically combining them rests largely on *In re Kerkhoven*: "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose…The idea of combining them flows logically from their having been individually taught in the prior art."

In *Kerkhoven*, the Court noted that the combination required "no more than the mixing together of two conventional spray-dried detergents." As previously noted by the Applicants, the compounds of Chamberlain et al. and the antigens or vaccine compositions of Klaviniskis et al. operate by quite different mechanisms and target different patient populations, a vaccine being primarily preventive, while a small molecule agent is ordinarily used as a treatment. The two categories are well known to require different formulations and administration routes and schedules.

Mixing them together is entirely unlike mixing the detergents in *Kerkhoven*. One of ordinary skill knows this, and would not have been motivated to mix them together without some expected advantage. The Examiner has identified *no expected advantages* provided by the mixture, and those skilled in the art know would not consider mixing a small molecule agent and a vaccine composition together to be comparable to mixing detergents.

Of more relevance to the question of admixing pharmaceutical agents is *Ex parte El-Naggar*, a precedential Board of Patent Appeals and Interferences opinion issued post-*KSR*. The issue in this case concerned the obviousness of a claimed pharmaceutical composition comprising a combination of three therapeutic agents (i.e., a COX-2 inhibitor, low dose aspirin, and an antioxidant), each of which was known separately in the prior art for the treatment of arthritis. The cited art taught the use of two of these agents in combination with other ingredients. In spite of the open transitional language "comprising", the Board concluded it would not have been obvious to include all the ingredients in the amounts disclosed in a single composition, and noted that "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986). The Board cited *KSR* in concluding that "[a]s is clear from cases such as [*United States v. Adams*, 383 U.S. 39 (1966)], a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, know in the prior art."

In the instant case, the cited art fails to suggest that the compounds of Chamberlain et al. (or oil-in-water emulsions thereof) have adjuvant activity or should be combined with immunogenic compositions, or that the *B. subtilis* spores of Klaviniskis et al. are replaceable by another adjuvant. Thus, the cited art, alone or in combination, provides no guidance that would lead one of skill in the art to conclude that physically combining a compound of Chamberlain et al. with an antigen of Klaviniskis et al would be reasonably likely to result in an enhanced immune response to the antigen. Moreover, even if a compound of Chamberlain et al. was for some reason physically admixed with a vaccine composition, nothing in the cited art would lead one of skill in the art to conclude that the compound would *necessarily* be present in an amount effective to enhance an

immune response to an antigen, as required to inherently meet the express claim limitations. *See* Valiante Declaration (already of record) at, e.g., ¶11.

Moreover, the Valiante Declaration has supplied reasons why one skilled in the art would not have combined the art cited by the Office in the essential manner the Applicants have done. See Valiante Declaration at, e.g., ¶¶ 8-10. This evidence has been improperly disregarded by the Office, and should also be sufficient to compel withdrawal of the rejection.

The cited art fails to provide a reasonable expectation of success

The Examiner asserts that "one of ordinary skill in the art would have had a reasonable expectancy to successfully make a composition comprising the active agent disclosed by Chamberlain et al. and the antigen and adjuvant disclosed by Klaviniskis, that would effectively treat breast cancers by stimulating the immune system and enhancing an immune response, with providing slow release of the antigen." (Office Action at pages 6-7.) The Examiner further states that: "[c]ombining two compositions for the same purpose of treating cancer does not need to focus on such minor details such as toxicities, tolerability, efficacy, and bioavailability. These details are the burden placed on the Applicant to show that such combination does not have a reasonable expectation of success. In the present case, there is no factual evidence regarding the toxicities, tolerability, efficacy, and bioavailability of the combination provided by the cited prior art." (emphasis added).

The Applicants must again respectfully disagree. The Examiner has the initial burden of establishing both a motivation to combine the cited references and a reasonable expectation of success in order to establish a *prima facie* case of obviousness. Contrary to the Examiner's unsubstantiated assertion, considerations of toxicity, tolerability, efficacy, and bioavailability are precisely the types of issues that a person of skill in the art would consider in determining whether a proposed composition or combination of agents has a reasonable expectation of success. These considerations are hardly *minor details*, as one of ordinary skill in the art seeking to treat a patient having cancer would clearly understand that these considerations are essential to the development of a successful treatment.

The Office has improperly disregarded objective evidence of nonobviousness

The Examiner has failed to properly consider the objective evidence of nonobviousness presented in the Valiante Declaration under 37 C.F.R. § 1.132, filed May 4, 2009. The Examiner asserts the evidence presented is insufficient to overcome the rejection of claims 21, 24, 26, 36-39 over Chamberlain et al. in view of Klaviniskis et al., on the grounds that "the arguments presented in the declaration are essentially the same ones presented throughout prosecution" and that "no factual evidence has been presented nor does the Valiante Declaration show evidence of the state of the prior art. In the absence of these types of evidence, response to the arguments is deferred to the above discussion regarding obviousness." Applicants respectfully submit that this is not a proper basis for disregarding properly presented rebuttal evidence.

"In assessing the probative value of an expert opinion, the examiner must consider the nature of the matter sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 227 USPQ 657 (Fed. Cir. 1985), *cert. denied*, 475 U.S. 1017 (1986). See also *In re Oelrich*, 579 F.2d 86, 198 USPQ 210 (CCPA 1978) (factually based expert opinions on the level of ordinary skill in the art were sufficient to rebut the *prima facie* case of obviousness)." MPEP 716.01(c)(III).

Dr. Valiante, the inventor of the present application, is a recognized expert in the field of vaccine discovery. Accordingly, he is eminently qualified to provide evidence on both the state of the prior art and the level of skill of ordinary practitioners in the area of vaccine formulations.

As evidenced by the Valiante Declaration, it is well known in the art that vaccine compositions are <u>not</u> ordinarily combined with small molecule therapeutic agents and that mixing an immunogenic composition and a therapeutic agent into a single composition would limit the ability to optimize the frequency and route of administration for each agent. *See* Valiante Declaration at ¶8. In addition, one of ordinary skill in the art would recognize that mixing such agents could lead to adverse drug interactions, for example, by eliciting an immune reaction to a

drug physically admixed with the vaccine composition. *See* Valiante Declaration at ¶9. For at least these reasons, the evidence of record demonstrates that a skilled practitioner in this art would not combine a vaccine and a small molecule drug like into a single composition unless there was some compelling reason to do so. *See* Valiante Declaration at ¶9. The Office has failed to identify any expected advantage of making such a physical combination that would lead one of skill in the art to do so, in view of the disadvantages cited above.

Moreover, as evidenced by the Valiante Declaration, one of skill in the art would understand that concurrent treatment with a vaccine and another therapeutic agent would not require mixing these materials together, *See* Valiante Declaration at ¶10. In view of the expected differences in routes and schedules of administration and the potential for adverse interactions, a person of skill in the art ordinarily would *not* mix such agents together. *See* Valiante Declaration at ¶10. Where concurrent treatment is desired, a skilled practitioner would preferably administer each agent to a single patient *separately*, allowing vaccine and small molecule agents to be delivered under optimal conditions and reducing the likelihood of adverse interactions. *See* Valiante Declaration at ¶10.

The Examiner has provided no evidence to rebut the declaratory evidence regarding the state of the art presented in the Valiante Declaration, nor cited a single reference in which a small molecule therapeutic agent was in fact combined with a vaccine composition for administration to a subject. In the absence of such rebuttal evidence, a conclusion of obviousness is inappropriate, because the evidence presented by the Applicants would have left a person of ordinary skill with unrebutted reasons not to combine the reference teachings in the manner claimed.

The Applicants respectfully request that the Examiner provide the factual basis for contradicting the evidence of record regarding the state of the prior art, as evidenced by the Valiante Declaration. If the Examiner's position relies on facts within the Examiner's personal knowledge, it is respectfully requested that the Examiner clearly identify this as the basis for support and provide an affidavit to that effect to make the record complete for appeal. 37 CFR 1.104(d)(2).

Evidence of unexpected rebuts any *prima facie* case of obviousness

Because a *prima facie* case of obviousness has not been established, Applicants have no burden to provide rebuttal evidence. Nevertheless, the record provides substantial evidence rebutting a conclusion of obviousness.

The claimed benzazole compounds of formula XXI produce an unexpected immune-stimulating response or agonistic effect to an antigen in the claimed compositions. *See* Valiante Declaration at ¶12. These compounds enhance the immune response elicited by an antigen, an effect which was not disclosed or suggested in the prior art. As evidenced by the Valiante Declaration, these effects could not have been expected from the cited documents, which disclose only antiangiogenic or antagonistic activity for the compounds of Chamberlain et al. *See* Valiante Declaration at ¶12. Thus, the compositions as claimed would not have been expected to provide an enhanced immune response to an antigen without the addition of an adjuvant. The discovery that the claimed compositions are unexpectedly effective without an adjuvant overcomes any alleged basis for an obviousness rejection.

The determination of obviousness or nonobviousness must be made in view of all of the evidence of record. When rebuttal evidence is presented for an alleged *prima facie* case of obviousness, the Examiner must consider all of the evidence before arriving at an ultimate conclusion. MPEP § 2145. Because the instant specification and Valiante Declaration provide evidence of unexpected results, a conclusion that the claimed invention would have been obvious is rebutted.

In view of the foregoing, Applicants respectfully request that the rejections under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 223002107200. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: December 3, 2009

Respectfully submitted,

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